UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,559	10/15/2004	Tim Jones	MER-133	4176

2387 7590 01/10/2006

OLSON & HIERL, LTD.
20 NORTH WACKER DRIVE
36TH FLOOR
CHICAGO, IL 60606

EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 01/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/511,559	JONES ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-13,17-21,24 and 25* is/are pending in the application.

4a) Of the above claim(s) *6,7,12,13,19 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,9,11,17,18,20,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendment received October 20, 2005 are acknowledged.

Claims 10, 14-16, 22,and 23 are canceled.

Claims 18-20 have been amended.

Claim 25 has been added.

Claims 1-9, 11-13, 17-21, 24, and 25 are pending in the instant application.

Applicant's election with traverse of Group I, claims 1-9, 11, 17-21, 24 and new claim 25 as they read of FVIII polypeptides with reduced immunogenicity, and the species election of the P7 epitope (AA 817-831 of SEQ ID NO:73) with the point mutation V823A in the reply filed on October 20, 2005 is acknowledged. The traversal is on the ground that claims 12 and 13 should be rejoined to the elected group. This is not found persuasive because of the reasons of record set forth in the restriction requirement mailed September 20, 2005. Specifically, the products of Group II are limited to peptides of 13 amino acids, whereas the products of Group I are drawn to FVIII molecules containing mutated sequences that reduce their immunogenicity yet still allow the molecules to participate in the blood coagulation cascade. Peptides of only 13 amino acids are not active in the coagulation process and have different utilities, since peptides can be used in screening methods but cannot substitute for the full length FVIII molecules of Group I in methods of administration to treat hemophilia. As such the products are patentably distinct.

The requirement is still deemed proper and is therefore made FINAL.

Claims 6, 7, 12, 13, 19, and 21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions and species. Applicant timely traversed the restriction (election) requirement in the reply filed on October 20, 2005.

Claims 1, 2, 3, 4, 5, 8, 9, 11, 17, 18, 20, 24, and 25 are under examination as the read on FVIII polypeptides comprising the epitope of residues 817-831 of SEQ ID NO:73 with the specific point mutation V823A. This specific mutation does not appear to be disclosed in the prior art, and as such the search has been extended beyond the elected species.

The examiner acknowledges receipt of the search report from the international bureau. If applicant wishes references cited in the search report to be listed on the face of an issued patent, these references should be submitted in an Information Declaration Statement. Please note that the references listed in the search report have not been forwarded from the international bureau, and as such a courtesy copy is requested if applicant chooses to list said references as part of an IDS.

Priority

2. It is noted that the instant application claims foreign priority to two European Patent Office documents, 02008712.8 filed 4/18/2002, and 03006554.4 filed 3/24/2003. All claims subsequent to base claim 1 appear to recite sequences found in either Table 1 or Table 2 of the instant specification. These sequences are 15 or more amino acids in length. The disclosure of the foreign priority document 02008712.8 filed 4/18/2002 does not appear to disclose any sequence longer than 13 amino acids, but the sequences disclosed in Tables 1 and 2 of the instant specification do appear to be disclosed in foreign priority document 03006554.4 filed 3/24/2003. Further, while 03006554.4 does provide the sequence of the P7 peptide it does not appear to provide guidance or direction to the specific substitution of the valine at position 823 of SEQ ID NO:73 to the other specifically recited amino acid residues, nor does it appear to provide such guidance for where substitutions should occur in other FVIII T cell epitope sequences that have been disclosed. Additionally, the method by which the activity of a modified FVIII molecule is to be assayed as is recited in instant claim 9 does not appear to be disclosed until the filing of foreign priority document 03006554.4. Therefore, the dates given to the instant claims for their examination in relation to the prior art is as follows:

04/18/2002 – Claims 1 and 11

03/24/2003 – Claims 2-4 and 9

04/17/2003 – Claims 5, 8, 17, 18, 20, 24, and 25

Note that claim 17 recites a full length sequence of a B domain deleted FVIII molecule, and that the foreign priority documents appear to disclose only short peptides and not a full length sequence that participate in the process of blood coagulation. Any amendments made to the instant claims in response to this office action may necessitate a redetermination of appropriate priority dates for claimed subject material.

Drawings

3. The drawings filed on October 15, 2004 are objected to because Figure 1 lists a multitude of sequences that are not identified by SEQ ID number either in the figure itself or in the Brief description of Figure 1 presented on page 25 of the instant specification. Applicant is reminded that if the instant application does not have an appropriate SEQ ID NO: for each disclosed sequence, then Applicant must comply with the Sequence Rules as set forth in 37 CFR 1.821-1.825. Appropriate correction is required.

Specification

4. Applicant is thanked for the amendments to the specification to correct issues of sequence compliance and to update the first line of the specification received October 15, 2004. However, it is noted that this amendment contains minor errors. Specifically, the section dealing with the sequence listing on compact disk contains a misspelling of the word "containing" and does not indicate a numerical size for the file in bytes. Appropriate correction is required.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 1-5, 8, 9,11, 17, 18, 20, 24, and 25 are rejected under 35 U.S.C. 101 because the claimed subject matter is non-statutory. Specifically, it is known that naturally occurring mutations in the human FVIII can give rise to polypeptides having the desired characteristics, as is evidenced by the teachings of Jacquemin et al. (Blood, 2003, 101:1351-1358, see entire document) wherein a naturally occurring mutant of FVIII is disclosed that has reduced immunogenicity due to the removal of a T cell epitope. Amendment of the claims to indicate involvement of the hand of man, such as through words such as "isolated, " "purified, " or other appropriate language that has support in the instant specification, would be beneficial in removing this rejection.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 8, 9, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 20 are rejected because the metes and bounds of the claims are not clear. Claim 8 recites a modified Factor VIII polypeptide with substitutions at *one, more or all* of a list of mutations. However, the recited substitutions all take place at position 823 of SEQ ID NO:73, wherein the wild-type valine is substituted for numerous recited residues. It is not clear to the examiner how a single polypeptide molecule can simultaneously have multiple amino acids at a single disclosed position unless these are multiple insertion mutations rather than substitutions as recited. Similarly, claim 20 is recited as having *at least one* of the recited substitutions and it is unclear how it is possible that the claimed polypeptide could have any more than one substitution at position 823.

Claim 9 is rejected because it the recitation of "the protein" at the end of line 5 and "protein" at the beginning of line 7 of claim 9 render the claim indefinite since the identity of the recited protein is not clear. Are these proteins the modified FVIII molecule, the wild-type human FVIII molecule, or something else entirely?

Appropriate clarification and or amendment of the claims are required.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-5, 8, 9,11, 17, 18, 20, 24, and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant has claimed FVIII molecules that have a different sequence from wild type human FVIII, with the sequence differences encompassing the removal of a T cell epitope. It is disclosed that an epitope is removed when in its mutated form the epitope sequence can no longer be bound by MHC class II molecules. Applicant discloses numerous peptides thought to be bound by MHC class II molecules that can evoke a proliferative T cell response in Tables 1 and 2 of the instant specification, and has an example wherein single amino acid substitutions at position 823 of FVIII are tested for their ability to be efficiently expressed and for biological activity in a clotting assay (see particularly from line 30 of page 41 to line 2 of page 43). Applicant discloses that the valine (V) at position 823 is a potential anchor residue important for binding to MHC class II molecules, and discloses that the amino acids A, C, D, E, K, N, P, Q, R, S, and T can also serve as potential primary anchor residues (see particularly lines 34 and 35 of page 41 of the instant specification). Residue 823 was chosen based on computer simulations of MHC class II binding, but no experimental data appears to be provided to confirm that V823 is an anchor residue important for binding to MHC class II molecules and that substitutions of this amino acid residue actually inhibit MHC class II binding or reduce the proliferative response elicited from FVIII-specific T cell clones (see particularly the paragraph that spans pages 26 and 27, and Figure 9).

Applicant has claimed modified FVIII sequences with reduced immunogenicity, some of which incorporate specific substitution mutations at position 823 of FVIII.

These recited substitution mutations include the replacement of V823 with A, D, E, G, H, N, P, S, and T. It is particularly noteworthy that the specification teaches that amino acid residues including A, D, E, N, P, S, and T can all act as primary anchor residues (see lines 34 and 35 of page 41). As such it appears that replacement of V with any one of these residues results in exchanging one anchor residue for another. Based on the teachings of the specification concerning the identity of amino acids that can serve as anchors, one would expect that FVIII molecules containing A, D, E, N, P, S, or T in place of V at position 823 would still bind MHC class II molecules and thus still be T cell epitopes.

All of the epitopes in FVIII identified by applicant, as well as the putative anchor residues within these epitopes that are necessary for binding to MHC class II molecules, are disclosed by applicant as having been identified by a computer program. It is known that different class II molecules bind different amino acid sequences and that there may be multiple binding sequences in FVIII for one class II molecule and none for another (White et al., Haematologica, 2000, 85:113-116, see entire document). Predicting the binding of a peptide to an MHC class II molecule is a difficult process complicated by the size heterogeneity peptides bound by MHC class II ligands, and predictions are far from perfect (Nielsen et al., Bioiformatics, 2004, 20:1388-1397, see entire document, particularly the first sentence of the paragraph that spans the left and right columns of page 1396). Indeed, many studies have predicted peptides that cannot be observed to bind to MHC class II molecules when experimentally tested (Cocholvius et al., J. Immunol., 2000, 165:4731-4741, see entire document, particularly Table I,

Figure 3, and the paragraph that spans the left and right columns of page 4738). As such, identification of MHC class II binding epitopes can be greatly aided by predictive computer programs, but the current state of such predictions is that they still require laboratory experiments to verify the accuracy of the prediction (Cocholvius et al., see particularly the first full paragraph of the left column of page 4739 and the first sentence of the last paragraph in the right column of page 4739). As such, it appears that the determination of MHC class II binding cannot be predicted based only upon *in silico* methodologies.

Further, substitutions designed to eliminate binding of an epitope to one particular MHC class II molecule may end up creating a new epitope that is capable of binding to some other MHC class II molecule (Jones et al., J. Thromb. Haemost. 2005, 3:991-1000, see entire document, particularly the last 3 sentences of the paragraph that spans pages 998 and 999). As such, mutating the sequence of FVIII may actually result in a molecule that has increased immunogenicity as compared to the parent molecule. Even if such mutations do not generate a new T cell epitope, they may introduce a new B cell epitope (Jones et al., see particularly the second complete sentence of the left column of page 999). B cell epitopes can result in the production of inhibitory antibodies that bind FVIII, and such unwanted antibody responses are a major problem in the treatment of many hemophilia patients (White et al., see entire document, particularly the abstract). Additionally, many deleterious substitution mutations in FVIII have been identified in hemophilia patients, some of which are located in positions indicated by applicant as desirable amino acids to mutate, such as positions 198 and 201 of SEQ ID

NO:73 (see printouts of the FVIII point mutation database listing downloaded from the HAMSTeRS database at europium.csc.mrc.ac.uk/WebPages/Main/main.htm), and it is known that the phenotypic results of a mutation in FVIII, such as alteration of biological activities, are correlated more with the position of the amino acid change within the 3D structure rather than with the identity of the actual alteration itself (Cutler et al., Human Mutation, 2002, 19:274-278, see entire document, particularly the abstract). Therefore, it does not appear likely that many of the positions recited for substitution mutagenesis by applicant such as those in claims 5 and 18 would permit modified FVIII molecules to have the same specificity and activity when used *in vivo*.

Therefore, based upon the fact that different class II molecules bind different peptide sequences and that the particular class II alleles bound by the epitopes of the instant invention are not recited, the fact that prediction of epitopes that bind to MHC class II molecules with computer programs is not predictable since putative epitopes must still be validated experimentally, the fact that the breadth of applicant's claims reads on mutations to FVIII in general as well as in specific locations, the apparent lack of experimental binding data to verify that V823 (and many positions recited in claims 5 and 18 for example) is an MHC class II anchor residue and that substitutions of this amino acid decrease binding, the fact that mutations made in an attempt to decrease immunogenicity may lead to the introduction of new epitopes that are capable of binding MHC class II molecules, the fact that mutations may introduce new B cell epitopes and thus increase overall immunogenicity or otherwise alter the biological activity and specificity of FVIII when used *in vivo* due to alteration of the 3D structure of FVIII, a

skilled artisan would be unable to make and use applicant's claimed invention without conducting additional research.

11. Claims 1-5, 8, 9,11, 17, 18, 20, 24, and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant's claims broadly read on all FVIII molecules that contain an amino acid sequence that is different from wild type FVIII such that the binding of a T cell epitope to an MHC class II molecule is reduced or eliminated. Applicant has also recited some specific locations within FVIII that are thought to be suitable for substitution mutagenesis to decrease immunogenicity and MHC class II binding. To support the claimed genus of modified FVIII molecules, applicant has disclosed the generation of substitution mutants for the epitope comprising amino acid V823. These molecules were tested for expression and clotting activity but were not tested for MHC class II binding or for the ability to induce a proliferative T cell response (see particularly Figure 7). Applicant discloses that a computer program is to be used to identify MHC class II binding epitopes and to identify substitution mutations that reduce binding (see particularly the paragraph that spans pages 26 and 27 and Figure 9). It does not appear that data has been provided that verifies the accuracy of the computer predictions with regard to MHC class II binding.

Many point mutations in FVIII are known, most of which are deleterious for biological activity, presumably due to disturbances in the 3D structure of the FVIII molecule (see printouts of the FVIII point mutation database listing downloaded from the HAMSTeRS database at europium.csc.mrc.ac.uk/WebPages/Main/main.htm and Cutler et al., Human Mutation, 2002, 19:274-278, see entire document, particularly the abstract). It is also known that computer algorithms used to predict binding to MHC class II molecules are far from accurate, and that experiments must be performed to verify the ability of any putative epitope to be bound by MHC class II molecules and recognized by T cells (Nielsen et al., Bioiformatics, 2004, 20:1388-1397, see entire document, particularly the first sentence of the paragraph that spans the left and right columns of page 1396 and Cocholvius et al., J. Immunol., 2000, 165:4731-4741, see entire document, particularly Table I, Figure 3, the paragraph that spans the left and right columns of page 4738, the first full paragraph of the left column of page 4739 and the first sentence of the last paragraph in the right column of page 4739). It is also known that substitution mutations in FVIII can increase the immunogenicity of the molecule, either through the introduction of new MHC class II binding epitopes that can be recognized by T cells or by the introduction of novel B cell epitopes that elicit an antibody response (Jones et al., J. Thromb. Haemost. 2005, 3:991-1000, see entire document, particularly the top of the left column of page 999).

Given all of the above, including the apparent lack of data verifying that the disclosed mutations to FVIII at all positions result in both reduced immunogenicity and in maintenance of biological activity of FVIII, a skilled artisan would reasonably conclude

that applicant was not in possession of the claimed genus of modified FVIII molecules that retain the biological activity of FVIII yet are less immunogenic due to substitution mutations that reduce MHC class II binding of T cell epitopes. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Before setting forth the art rejections, it is important to remember that not all of the claims under examination have the same date with regard to the prior art. The appropriate dates as discussed above are:

04/18/2002 – Claims 1 and 11

03/24/2003 – Claims 2-4 and 9

04/17/2003 – Claims 5, 8, 17, 18, 20, 24, and 25.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 1 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Tiarks et al. (Scand J Immunol, 1992, 36:653-660, see entire document).

Tiarks et al. teach that recombinant FVIII molecules are to be made containing mutations which decrease the immunogenicity of epitopes recognized by T helper cells (see entire document, particularly the abstract). Such mutations are taught as reducing the ability of the peptide epitopes to bind MHC molecules and as not interfering with the biological function of FVIII (see particularly page 658). Recombinant FVIII molecules with reduced immunogenicity are better suited than wild-type FVIII for the treatment of diseases such as hemophilia A since the mutant recombinant forms will elicit a diminished anti-FVIII inhibitory antibody response (see particularly the Introduction section on page 653).

Therefore, the prior art anticipates the instant invention.

14. Claims 2-4, 9, 17, and 24 are rejected under 35 U.S.C. 102(a) as being anticipated by Jacquemin et al. (Blood, 2003, 101:1351-1358, see entire document, available online October 17, 2002).

Jacquemin et al. teach a FVIII molecule isolated from a hemophilia patient that contains a point mutation that eliminates a T cell epitope and thus makes the molecule less immunogenic (see entire document, particularly the abstract). This point mutation

causes a reduction in the ability of the T cell epitope to be bound by MHC class II molecules (see particularly Table 3 and the first full paragraph of the right column of page 1356). This point mutation occurs in an epitope sequence found in the list of epitopes disclosed in Tables 1 and 2 of the instant specification.

It is noted that Jacquemin et al. measured T cell activation in response to modified FVIII molecule rather than proliferation as is recited in claim 9. However, given that the mutant FVIII disclosed by Jacquemin et al. causes less T cell activation as measured by a cytokine release assay, it is inherent that this molecule also causes a diminished T cell proliferative response since its ability to be recognized by T cells is compromised as compared to wild type FVIII.

Therefore, the prior art anticipates the claimed invention.

15. Claims 2-4, 9, 17, and 24 are rejected under 35 U.S.C. 102(a and e) as being anticipated by WO 02/098454 A2 (see entire document).

WO 02/098454 discloses recombinant human FVIII that has been modified to remove one or more T cell epitopes such that the recombinant protein is less immunogenic for use in the treatment of diseases such as hemophilia (see entire document, particularly the abstract, lines 25-31 of page 6, lines 3-20 of page 8, and claims 1-30,47-51, 57, 73-79, 85, 86, 89, 90, 93-98, 102, and 103). Specific mutations disclosed include those within the p11 peptide sequence found in Tables 1 and 2 of the instant specification (see particularly Figures 1-5 and Examples 1-3). Mutations are disclosed as altering the binding of the T cell epitope to MHC class II (see particularly

lines 8-23 of page 23). Recombinant FVIII molecules are also disclosed as being present in pharmaceutical compositions (see particularly from line 24 of page 24 to line 21 of page 28).

Therefore, the prior art anticipates the claimed invention.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1-4, 9, 17, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tiarks et al. (Scand J Immunol, 1992, 36:653-660, see entire document) in view of Laub et al. (WO 96/02572A2, see entire document) as evidenced by the English language equivalent US Patent No. 6,866,848, see entire document). Note that all locations indicated for the teachings of Laub et al. refer to the '848 patent and not WO 96/02572.

The teachings of Tiarks et al. have been discussed above. These teachings differ from the instant invention in that while Tiarks et al. teach modifying the amino acid sequence of FVIII to make it less immunogenic, they do not disclose any specific epitopes of FVIII that are to be modified to generate FVIII molecules with reduced immunogenicity.

Laub et al. identify multiple immunogenic epitopes of FVIII that are recognized by the human immune system (see entire document, particularly the abstract and lines 60-67 of column 5). Many of these epitopes overlap with those disclosed in Table I of the instant specification, and one is completely contained within the peptide of residues 961-705 of Table I (see particularly lines 8-15 of column 10). The epitopes disclosed by Laub et al. offer the advantage that they are capable of being recognized by T cells and can be bound to MHC class II molecules (see particularly lines 43-52 of column 11 and lines 38-42 of column 12).

Therefore, a person of ordinary skill at the time the invention was made would have been motivated to modify the epitopes disclosed by Laub et al. and use them in the recombinant FVIII molecules disclosed by Tiarks et al. in order to gain the advantage of a recombinant FVIII molecule that contains T cell epitopes that have been modified to make the recombinant FVIII molecule less immunogenic so that it can be more effectively used in treating hemophilia A and other coagulation diseases since it is less likely to elicit an inhibitory antibody response.

Claim 9 has been included in this rejection since a recombinant FVIII molecule containing a mutated T cell epitope that is less able to elicit a neutralizing antibody

response inherently possess the characteristic of being less potent than wild-type FVIII in inducing the proliferation of T cells.

18. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael Szperka, Ph.D.
Patent Examiner
Technology Center 1600
December 28, 2005

Patrick J. Nolan, Ph.D.
Primary Examiner
Technology Center 1600
1/7/06